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Oren Becker

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EXAMINER

LIN, JERRY

ART UNIT

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/718,425	<b>Applicant(s)</b> BECKER ET AL.	
	<b>Examiner</b> Jerry Lin	<b>Art Unit</b> 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 18-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17 and 22-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Applicants' arguments, filed January 14, 2008, have been fully considered and they are not deemed to be persuasive. However, upon reconsideration of the claims, new grounds of rejection are required. The following rejections are reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

#### ***Claim Rejections - 35 USC § 112, 1<sup>st</sup> Paragraph***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Applicants have included new claim 24 to recite that the instant method does not utilize the dead-end algorithm. Applicants cite page 3, and page 4, lines 1-4 for support. Pages 3-4, beginning at the bottom of page 3, recite, "However, despite the success of these studies, a full predictive understanding of hydrophobic core packing in proteins has not yet been fully realized, and *de novo* design of stable and unique proteins, remains a challenging problem. A major breakthrough was achieved by the Dead-End

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Elimination (DEE) algorithm by Desmet et al. . . ." While the passage does describe the prior art, this passage does not disclose that the Dead-End Elimination algorithm is not used with the claimed method. Furthermore, neither the specification nor the original claims discusses that the dead-end elimination algorithm is not used. Since the limitation of the method not utilizing the dead-end algorithm does not appear in the originally filed specification or the original claims, new claim 24 is NEW MATTER.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> Paragraph***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "said input means" in line 12. There is insufficient antecedent basis for this limitation in the claim. Although the instant claim does recite "input apparatus", the instant claims do not mention the limitation "input means" previously in the instant claim

***Claim Rejections - 35 USC § 101***

5. 35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-17 and 22-24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The instant claims are drawn to a process involving the judicial exception of a computational algorithm. Claims drawn to a judicial exception is non-statutory unless the claims include a practical application of that judicial exception as evidenced by a physical transformation of matter, or if the claimed invention recites a useful, tangible and concrete final result. In the instant claims, there is no physical transformation by the claimed invention, thus the Examiner must determine if the instant claims produce a useful, tangible, and concrete final result. See MPEP 2106.

The instant claims do not require a tangible final result. A tangible final result requires that the claim must set forth a practical application of the mathematical algorithm to produce a real-world result. The instant claims end with a step of creating a computer output. However, a computer output does not necessarily mean that the output is communicated to the outside world. For example, the computer output could be in the form of a carrier wave. A carrier wave is not a tangible final result. Thus, the instant claims do not require a tangible final result. Examples of amendments to overcome this rejection include amending the claims to identify/recite a concrete result and to recite that the result is outputted to a display or to a user or outputted in a user readable format. However, applicant is reminded that any amendment must be fully supported and enabled by the originally filed disclosure.

Response to Arguments

7. The Examiner acknowledges that amending step g) in claim 1 to remove the term "optionally" to overcome this rejection was suggested. However, upon reconsideration of the claims, this rejection has been reapplied for the reasons above.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5, 9-17, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (Protein Science (1996) Volume 5, pages 895-903) in view of Herzyk et al. (Proteins) Volume 17, pages 310-324).

The instant claims are drawn to a method of predicting an amino acid sequence by providing a coordinate set representing the backbone of a 3D structure, constructing a reduced virtual representation for the 3D structure, determining the amino acid positions along the 3D structure, constructing an initial amino acid sequence, randomly selecting one or more positions along the sequence and applying a Monte-Carlo simulation, and expanding the reduced representation.

Regarding claims 1-5, 9-17, 22 and 23, Dahiyat et al. teaches protein design automation. Specifically they teach "We have conceived and implemented a cyclical protein design strategy that couples theory, computation, and experimental testing. The combinatorially large number of possible sequences and the incomplete understanding of the factors that control protein structure are the primary obstacles in protein design. Our protein design automation algorithm objectively predicts protein sequences likely to achieve a desired fold. Using a rotamer description of the side chains, we implanted a fast discrete search algorithm base on the Dead End Elimination Theorem to rapidly find the globally optimal sequence in its optimal geometry from the vast number of possible solutions. Rotamer sequences were scored for steric complementarity using a van der Waals potential. A Monte Carlo search was then executed, starting at the optimal sequence in order to find other high-scoring sequences. As a test of the design methodology, a high scoring sequences were found for the buried hydropobic residues of a homodimeric coiled coil base on GCN4-p1. The corresponding peptides were synthesized and characterized by DC spectroscopy and size exclusion chromatography. . . . A quantitative structure activity relation analysis was performed on the designed

peptides, and a significant correlation was found with surface area burial. Incorporation of the buried surface area potential in the scoring of sequences greatly improved the correlation between predicted and measured stabilities and demonstrated experimental feedback in a complete design cycle.” (Abstract). Specifically, Dahiyat also teaches that the PDA side-chain selection algorithm requires as input a backbone structure defining the desired fold. Also taught is that “using a rotamer description of side chains, an optimal sequence for a backbone can be found by screening all possible sequences of rotamers, where each backbone position can be occupied by each amino acid and all its possible rotameric states.” (page 896). (This corresponds to steps (a) through (d) of claim 1.) Also taught is “following DEE optimization, a rank-ordered list of sequences is generated by a Monte Carlo search in the neighborhood of the DEE solution. . . random position are changed to other rotamers, and the new energy is calculated. If the new sequence energy meets the Boltzmann criteria for acceptance, it is used as the starting point for another jump. . . after a predetermined number of jumps, the best scoring sequences are output as a rank-ordered list.” (Page 897). (This corresponds to step (e) of claim 1.) Also taught is that simpler structure measure, such as buried atoms, were used to resolve the structure of the amino acid. (page 899). (This corresponds to step (f) of claim 1.) Dahiyat et al. also teach using hydrophobic and hydrophilic positions to determine the structure (page 897). In regards to claims 10 and 11, since all positions are selected from the entire group of amino acids, Dahiyat et al. discloses the limitations of these claims. In regard to claim 23, Dahiyat et al. teaches using a computational



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method that would require use of a computer with an input apparatus, multiple memories, and a processor (page 901, right column).

However, Dahiyat et al. does not teach representing a protein wherein each amino acid has a backbone portion and side chain portion, where the backbone portion is represented by a single sphere and the side chain of each amino acid is represented by one to two additional spheres.

Regarding claim 1, Herzyk et al. teach representing (i.e. a computer output) a protein wherein each amino acid has a backbone portion and side chain portion, where the backbone portion is represented by a single sphere and the side chain of each amino acid is represented by one to two additional spheres. (Abstract; page 312 and throughout. See also specification at page 9, lines 3-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Dahiyat et al. and Herzyk et al. One of ordinary skill in the art could have taken the data of Dahiyat et al. and represented that data in the teachings of Herzyk et al. One of ordinary skill in the art could have combined the elements as claimed by known methods with no change in their respective functions. Furthermore, the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

#### Response to Arguments

10. Applicants have responded by questioning the motivation to combine the references. However, the decision in KSR forecloses the argument that a specific

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teaching, suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith*, --USPQ2d--, slip op. at 20. (Bd. Pat. App. & Interf. June 25, 2007).

Applicants also state that their method does not use the dead-end elimination algorithm. However, this limitation is not in the claims and cannot be used to distinguish it from the prior art.

Applicants also argue that their method yield a high resolution protein structure. However, this limitation is not in the claims and cannot be used to distinguish it from the prior art. The claims are broadly read to include outputs of any resolution.

11. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (Protein Science (1996) Volume 5, pages 895-903) in view of Herzyk et al. (Proteins) Volume 17, pages 310-324) as applied to claims 1-5, 9-17, 22 and 23 above, and further in view of Hurley et al. (JMB Vol. 224, 1992, pages 1143-1159).

Dahiyat et al. and Herzyk et al. are applied as above.

However, neither Dahiyat et al. nor Herzyk et al. teaches that the solvent is substantially water.

Regarding claims 6-8, Hurley et al. teaches design and structural analysis of alternative hydrophobic core packing arrangements in bacteriophage T4 lysozyme. Particularly, they teach, "in order to calculate stability changes in aqueous solution, the changes in free energies of transfer of the folded and unfolded states between water and vacuum must be obtained." (Page 1146).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teaching of Dahiyat et al., Herzyk et al., and those of Hurley et al. As Hurley et al. teach, it would have been obvious to determine the structure of an amino acid in water because it would have allowed for the calculation of stability change. Also, water would have been a common solvent for the amino acid structures to be found in nature, and therefore would have been obvious to use as it would have allowed for the closest approximation to nature. Furthermore, water would have been obvious solvent due to its neutral pH, low cost, and easy availability.

#### Response to Arguments

12. Applicants have responded to his rejection by relying on their response to Dahiyat et al. and Herzyk et al. Please see above for the examiner's response.

#### ***Withdrawn Rejections***

13. Applicant's arguments and amendments, filed January 14, 2008, with respect to the rejections made under 35 U.S.C. §112 2nd Paragraph have been fully considered and are persuasive. The amendment overcome the rejections made under 35 U.S.C. §112 2nd Paragraph in Office Action mailed 7/18/2007. These rejections have been withdrawn.

#### ***Contact Information***

Art Unit: 1631

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571)272-2561.

The examiner can normally be reached on 7:00-5:30pm, M-TH.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jerry Lin/  
Examiner, Art Unit 1631  
4/24/2008